Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System

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Subcutaneous allergen immunotherapy (SCIT) is an effective treatment for allergic rhinitis, asthma and venom hypersensitivity and has the potential of producing serious life-threatening anaphylaxis. Adverse reactions are generally classified into 2 categories: local reactions, which can manifest as redness, pruritus, and swelling at the injection site, and systemic reactions (SRs). SRs can range in severity from mild rhinitis to fatal cardiopulmonary arrest. Early administration of epinephrine, which is the treatment of choice to treat anaphylaxis, may prevent the progression of an SR to a more serious life-threatening problem. Although there is little debate about using epinephrine to treat a SCIT SR, there is a lack of consensus about when it should be first used. A uniform classification system for grading SCIT SRs will be helpful in assessing more accurately when epinephrine should be administered. The primary purpose of this article is to discuss the proposed grading system for SCIT SRs. (J Allergy Clin Immunol 2010;125:569-74.)

Key words: *Subcutaneous allergen immunotherapy, anaphylaxis grading system, systemic reaction grading system, allergic rhinitis, asthma*

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Abbreviations used

AAAAI: American Academy of Allergy, Asthma & Immunology
ACAAI: American College of Allergy, Asthma & Immunology
BP: Blood pressure
EAACI: European Academy of Allergy and Clinical Immunology
PEF: Peak expiratory flow
SCIT: Subcutaneous immunotherapy
SR: Systemic reaction
WAO: World Allergy Organization

Subcutaneous allergen immunotherapy is the administration of gradually increasing quantities of an allergen vaccine to an allergic subject, reaching a dose that is effective in ameliorating the symptoms associated with the subsequent exposure to the causative allergens.[1] Subcutaneous immunotherapy (SCIT) was established nearly 100 years ago when Noon and Freeman began "inoculating" grass-pollen allergic patients with grass pollen extracts.[2] Multiple controlled clinical trials demonstrate that SCIT is effective to treat allergic asthma, allergic rhinitis, and stinging insect hypersensitivity. SCIT may be useful to treat aero-allergen-induced atopic dermatitis.[3-6] It also may prevent the progression of allergic disease[7,8] and provide lasting benefits after discontinuation.[9]

Adverse SCIT reactions are generally classified into 2 categories: local reactions, which can manifest as erythema, pruritus

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Disclosure of potential conflict of interest: D. Larenas-Linnemann receives honoraria from Schering-Plough and MSD, receives grants from ALK-Abelló and Stallergenes, and receives research support from ALK-Abelló, Stallergenes, and Alerquim de Mexico. S. Dreborg receives grant support from ALK-Abelló, Hørsholm, Denmark; has provided legal consultation/expert witness testimony for MEDECA Pharma AB Sweden; and serves on the editorial boards of *Pediatric Allergy and Immunology* and the *Annals of Allergy, Asthma, and Immunology*. D. Bernstein is a consultant for ALK-America and Schering-Plough, receives grant support from Schering-Plough, and is on the ACAAI Board of Regents. E. Valovirta is a lecturer for Merck, is a consultant for ALK-Abelló, receives honoraria from ALK-Abelló, and receives research support from Merck and Allergopharma. J. Bousquet is a member of the Stallergenes board and has received lecture fees from ALK. M. Calderon receives honoraria from ALK-Abelló, Denmark, and Schering-Plough and receives research support from ALK-Abelló, Denmark. D. Ledford owns stock in AstraZeneca and Merck; is a consultant for Novartis, Genentech, and Take Care Health Systems; is on the advisory board for Novartis, Genentech, and AstraZeneca; is a speaker for Novartis, Genentech, AstraZeneca, Schering, Merck, SepraCorp, SanofiAventis, and UCB; receives honoraria from Novartis, Genentech, AstraZeneca, Schering, Merck, SepraCorp, SanofiAventis, and UCB; and receives research support from Genentech, Forest, AstraZeneca, and Take Care Health Systems. H. Nelson is a consultant for Genentech, Novartis, Abbott, Medicinova, Amgen, Dyson, Sepracor, GSK, AstraZeneca, and Schering-Plough; is on the speakers' bureau for GlaxoSmithKline; and receives research support from Schering-Plough, AstraZeneca, Genentech, and Ception. The rest of the authors have declared that they have no conflict of interest.

The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System was developed by The Joint Task Force for Grading Systemic Reactions to Immunotherapy. Members of this task force include the editors of this article and the following authors listed alphabetically: David Bernstein, MD, Jean Bousquet, MD, Moises Calderon, MD, PhD, Walter Canonica, MD, Thomas B. Casale, MD, Sten Dreborg, MD, PhD, Dennis Ledford, MD, Harold Nelson, MD, and Erkka Valovirta, MD, PhD. The comments of Joint Task Force for Grading Systemic Reactions members and invited reviewers are posted in this article's Online Repository at www.jacionline.org.

Received for publication September 4, 2009; revised October 9, 2009; accepted for publication October 12, 2009.

Available online February 8, 2010.

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0091-6749/$36.00

doi:10.1016/j.jaci.2009.10.060

and swelling at the injection site; and systemic reactions (SRs). SRs can range in severity from mild to very severe life-threatening anaphylaxis. Although fatal SCIT reactions are rare, they continue to be reported at a rate of approximately 1 in 2 to 2.5 million injections in the United States on the basis of 3 surveys of American Academy of Allergy, Asthma & Immunology (AAAAI) members that span the period from 1945 to 2001.[10-12]

A 3-year joint AAAAI/American College of Allergy, Asthma & Immunology (ACAAI) anonymous internet-based Immunotherapy Safety Survey designed to determine the incidence rate of fatal or near-fatal reactions was begun in late 2008. This project also gathered information by using a novel grading system for SRs (see this article's Table E1 in the Online Repository at www.jacionline.org), on which the current proposed system presented in this article is based (Table I). An Excel spreadsheet is available online to assist in recording appropriately the grade of an SR, time of onset, and treatment (see this article's Table E2 in the Online Repository at www.jacionline.org).

Variability in how SCIT SRs are defined may lead to misinterpretations and difficulties in evaluating the safety of SCIT and other forms of allergen immunotherapy. In addition, various grading systems are used to report SCIT SRs, but none have been globally accepted. A uniform classification system for grading SCIT-associated SRs would be helpful to treat such reactions by assessing more accurately when epinephrine should be administered, for example, by comparing outcomes from clinical practices that administer epinephrine early versus those that administer it later during an SR. It will also facilitate comparison of outcomes from different clinical trials, making it possible to collect better surveillance data on immunotherapy safety and compare practice parameters with outcomes.

A multinational group emerged from the AAAAI-ACAAI coalition, now including the Immunotherapy Surveillance Safety Group of the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organization (WAO). A consensus was reached on an acceptable SCIT SR grading system that can be used in both clinical practice and research. The purpose of this article is to present this new grading system for SCIT-induced SRs.

DEFINITION OF ANAPHYLAXIS

In 2004 and 2005, the US National Institutes of Allergy and Infectious Diseases (Bethesda, Md) and the Food Allergy and Anaphylaxis Network (Chantilly, Va) convened an international and interdisciplinary symposium of 16 professional, government, and lay organizations: the Anaphylaxis Working Group. The purpose of this symposium was to establish clinical criteria that would increase the diagnostic precision to recognize anaphylaxis and evaluate the evidence to provide guidelines for its most appropriate management.[13] The group proposed that anaphylaxis is likely to be present clinically if any 1 of 3 criteria is satisfied, regardless of the time of onset. The fundamental criteria, abbreviated here, include the following: "…1. acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both … AND AT LEAST ONE OF THE FOLLOWING … Respiratory compromise … Reduced BP [blood pressure] or … End-organ dysfunction … 2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours): …Involvement of the skin-mucosal tissue… Respiratory compromise …Reduced BP or associated symptoms … Persistent gastrointestinal symptoms … 3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours): …Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP … Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline[13]…." The article includes the following signs and symptoms as components of anaphylaxis:

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
- End-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
- Cutaneous or mucosal (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
- Gastrointestinal (eg, crampy abdominal pain, vomiting)

The implication from this definition is that symptoms representing more than 1 organ system need to present before epinephrine is administered. Applying these criteria to SCIT SRs poses the risk of delayed administration of epinephrine as the clinician waits for the patient to develop symptoms of a second organ system. SCIT SRs, presenting as a single organ system, can be severe, such as laryngeal edema or severe bronchospasm, and mild reactions, such as generalized pruritus, can rapidly progress to life-threatening anaphylaxis. In both instances, delay in administration of epinephrine until the reaction fulfills the anaphylaxis definition criteria could have catastrophic consequences.

The Anaphylaxis Working Group report did include a caveat: "There undoubtedly will be patients who present with symptoms not yet fulfilling the criteria of anaphylaxis yet in whom it would be appropriate to initiate therapy with epinephrine, such as a patient with a history of near-fatal anaphylaxis to peanut who ingested peanut and within minutes is experiencing urticaria and generalized flushing."

In a WAO position paper entitled "Epinephrine: The Drug of Choice for Anaphylaxis: A Statement of the World Allergy Organization," anaphylaxis is defined as "…an acute and potentially lethal multisystem allergic reaction in which some or all of the following signs and symptoms occur: diffuse erythema, pruritus, urticaria and/or angioedema; bronchospasm; laryngeal edema; hypotension; cardiac arrhythmias; feeling of impending doom; unconsciousness and shock other earlier or concomitant signs and symptoms can include itchy nose, eyes, pharynx, genitalia, palms, and soles; rhinorrhea; change in voice; metallic taste; nausea, vomiting, diarrhea, abdominal cramps, and bloating; lightheadedness; headache; uterine cramps; and generalized warmth."[14] Such a reaction should be temporally associated with the administration of a known or suspected allergen or substance known to cause anaphylaxis.

The survival for patients who have an SR secondary to SCIT can depend on how an SR or anaphylaxis is defined. Systemic or anaphylactic reactions, as defined by the Anaphylaxis Working Group, imply that the administration of epinephrine is usually not indicated unless multiple symptoms are present—in particular, when there is hypotension or respiratory distress. The WAO definition supports the administration of epinephrine with any signs or symptoms associated with an SR after administration of a known allergen or a substance associated with such a reaction. In fact, the majority, but not all the authors of the "Epinephrine: The Drug of Choice for Anaphylaxis-A Statement of the World

TABLE I. World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System (see text)

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Symptom(s)/sign(s) of 1 organ system present* **Cutaneous** Generalized pruritus, urticaria, flushing, or sensation of heat or warmth† **or** Angioedema (not laryngeal, tongue or uvular) **or** **Upper respiratory** Rhinitis - (eg, sneezing, rhinorrhea, nasal pruritus and/or nasal congestion) **or** Throat-clearing (itchy throat) **or** Cough perceived to originate in the upper airway, not the lung, larynx, or trachea **or** **Conjunctival** Erythema, pruritus or tearing **Other** Nausea, metallic taste, or headache	***Symptom(s)/sign(s) of more than 1 organ system present*** **or** **Lower respiratory** Asthma: cough, wheezing, shortness of breath (eg, less than 40% PEF or FEV_1 drop, responding to an inhaled bronchodilator) **or** **Gastrointestinal** Abdominal cramps, vomiting, or diarrhea **or** **Other** Uterine cramps	**Lower respiratory** Asthma (eg, 40% PEF or FEV_1 drop NOT responding to an inhaled bronchodilator) **or** **Upper respiratory** Laryngeal, uvula, or tongue edema with or without stridor	**Lower or upper respiratory** Respiratory failure with or without loss of consciousness **or** **Cardiovascular** Hypotension with or without loss of consciousness	Death

Patients may also have a feeling of impending doom, especially in grades 2, 3, or 4.

Note: Children with anaphylaxis seldom convey a sense of impending doom and their behavior changes may be a sign of anaphylaxis; eg, becoming very quiet or irritable and cranky.

Scoring includes a suffix that denotes if and when epinephrine is or is not administered in relationship to onset of symptom(s)/sign(s) of the SR:a, ≤ 5 minutes; b, >5 minutes-to ≤10 minutes; c: >10 to ≤20 minutes; d:>20 minutes; z, epinephrine not administered.

The final grade of the reaction will not be determined until the event is over, regardless of the medication administered. The final report should include the first symptom(s)/sign(s) and the time of onset after the subcutaneous allergen immunotherapy injection*** and a suffix reflecting if and when epinephrine was or was not administered, **eg, Grade 2a; rhinitis:10 minutes**.

Final Report: Grade a-d, or z_____ First symptom(s)/sign(s)_____ Time of onset of first symptom_____

Comments:§

*Each grade is based on organ system involved and severity. Organ systems are defined as cutaneous, conjunctival, upper respiratory, lower respiratory, gastrointestinal, cardiovascular, and other. A reaction from a single organ system such as cutaneous, conjunctival, or upper respiratory, but not asthma, gastrointestinal, or cardiovascular is classified as a grade 1. Symptom(s)/sign(s) from more than one organ system or asthma, gastrointestinal, or cardiovascular are classified as grades 2 or 3. Respiratory failure or hypotension with or without loss of consciousness define grade 4 and death grade 5. The grade is determined by the physician's clinical judgment.

†This constellation of symptoms may rapidly progress to a more severe reaction.

***Symptoms occurring within the first minutes after the injection may be a sign of severe anaphylaxis. Mild symptoms may progress rapidly to severe anaphylaxis and death.

§If signs or symptoms are not included in the table or the differentiation between a SR and vasovagal (vasodepressor) reaction, which may occur with any medical intervention, is difficult, please include comment, as appropriate.

Allergy Organization" recommend that any signs or symptoms of anaphylaxis, such as generalized pruritus, erythema, urticaria, and angioedema alone, and any other systemic symptom including those not involving vital organs, again, when associated with the administration of a known or suspected allergen or agent, should be treated immediately with appropriate intramuscular doses of epinephrine in an attempt to prevent more severe anaphylaxis from occurring. Additional doses of epinephrine, other medications, and supportive care should be used depending on the clinical response.

SCIT SRS: INCIDENCE AND SYMPTOMS

A summary of the SCIT SR rates reported in studies published within the past 15 years is presented in this article's Table E3 in the Online Repository at www.jacionline.org. It is divided by geographic location, with the upper section representing allergy/immunology clinics in the United States and the lower section Europe. The percentage of SR per injection in conventional schedules is approximately 0.2% (range, 0.026% to 0.37% in the United States and 0.01% to 0.3% in Europe).

Although the signs and symptoms of the SR are documented in some reviews, most do not provide this detailed information. The most frequent signs and symptoms appear to be rhinitis and rhinoconjunctivitis, generalized pruritus, and cough. Shortness of breath, urticaria, and asthma are also frequently documented. Others include malaise, asthenia, fever, headache, dizziness, lightheadedness, itchy throat, difficulty swallowing, dyspnea, tightness of the chest, abdominal pain, nausea, vomiting, and generalized erythema. The order of frequency in a prospective study of SRs associated with prick-puncture and intradermal skin testing was pruritic eyes, nose, or pharynx, worsening cough,

sensation of difficulty swallowing, nasal congestion rhinorrhea, chest tightness or shortness of breath, generalized pruritus, sneezing, wheeze, and urticaria.[15]

SAFETY SURVEILLANCE SURVEYS: FATAL AND NEAR-FATAL REACTIONS

There were 41 fatalities from SCIT injections identified over a 12-year period (1990-2001) in an AAAAI survey of physician members.[10] Detailed characteristics of 17 cases were provided by physicians in a follow-up questionnaire. Fifteen of these 17 SCIT fatalities had asthma and asthma not optimally controlled, which was considered a susceptibility factor that contributed to the fatal outcomes in 9 of these cases.

The 1990 to 2001 survey also solicited information on near-fatal immunotherapy reactions, defined as respiratory compromise and/or hypotension requiring emergency epinephrine.[16] There were 273 incidents resulting in a near-fatal reaction rate of 23 per year, or 5.4 events/million injections (0.0054/1000 injections). "…Administration of injections during the height of the allergy season (46% of respondents)" and dosing error (25% of respondents) were the 2 most important contributing factors for these reactions.[16] Asthma was also identified as a risk factor, present in 4 of the 5 near-fatal reactors who experienced a cardiopulmonary arrest and all 7 patients who experienced respiratory compromise. The baseline FEV_1 values were less than 70% predicted in 4 of the 7 patients with near-fatal immunotherapy reactions who required intubation and 5 of 10 patients who experienced a fatal reaction.

Data were provided by 806 practices representing 1922 SCIT prescribers (>50% response rate) in a 3-year AAAAI/ACAAI Immunotherapy Safety Survey.[17] There were no fatalities reported in 2008 for the approximately 8.1 million injections administered. However, respondents voluntarily reported 6 SCIT fatalities from 2001 to 2007 that occurred in other practices.

Recognizing drawbacks of the existing SR grading system, the expanded committee collaborated to develop a universally accepted SCIT SR grading system.

CURRENT CLASSIFICATION SYSTEMS FOR GRADING SCIT SR: HISTORY AND DRAWBACKS

Lockey et al[18] devised an SR index by using a numerical scale devised for ranking of severity of SRs (see this article's Table E4 in the Online Repository at www.jacionline.org). Signs or symptoms such as unconsciousness, shock, drop in blood pressure, lower airway obstruction, upper airway obstruction, gastrointestinal symptoms, angioedema/urticaria, pruritus, and others were each given a numerical ranking so that the sums of values for a mild reaction would not equal the lowest value of a moderate reaction, and the sum of values of moderate reaction, either alone or in conjunction with a mild reaction, would not equal the value of the least of the severe reactions (drop in blood pressure).[18] This was one of the first attempts to separate mild, moderate, and severe reactions, in this case, from *Hymenoptera* stings.

The EAACI published a position paper on SCIT in 1993, which included a proposed SR grading system from 0 to 4, commonly referred to as the Müller system (see this article's Table E5 in the Online Repository at www.jacionline.org).[19] Grade 0 indicates no symptoms, and grade 1 represents symptoms not likely to be associated with a SCIT injection, such as headaches or arthralgias. Grades 2 through 4 are described as "mild SR," "non-life-threatening SR," and "anaphylactic shock," respectively.

These grade definitions include the observed responses to treatment: grade 2 reactions are "mild rhinitis or asthma symptoms responding adequately to anti-histamines or $beta_2$-agonist spray," grade 3 reactions are "urticaria, angioedema, or severe asthma responding well to treatment," and grade 4 reactions are "rapidly evoked reactions of itching, flushing, erythema, bronchial obstruction, etc. requiring intensive treatment."[19] The specific treatments for grades 3 and 4 are not specified for this system, but the EAACI position paper recommends β_2-agonist and oral corticosteroids for "…mild to moderately severe bronchial obstruction…" and subcutaneous or intramuscular epinephrine for "serious reactions."[19]

The EAACI Immunotherapy Task Force in 2006 proposed a "more operational" grading system which was based on the time of onset and severity of an SR (see this article's Table E6 in the Online Repository at www.jacionline.org).[20] Grade 0 indicates no reaction, whereas grade 1 is a "mild systemic reaction," associated with less than 20% drop in PEF. Grades II and III are cutaneous and respiratory reactions of increasing severity that specify the time of onset of symptoms and the percentage of drop in PEF.

Grade II is a "Slow onset (greater than 15 min) of generalized urticaria and/or moderate asthma and a PF [*sic,* PEF] decrease of less than 40% from baseline." Grade III is the "Rapid onset (less than 15 min) of generalized urticaria, angioedema, or severe asthma and a decrease in PF [*sic,* PEF] of more than 40% from baseline." Grade IV, or "Anaphylactic shock," is defined as the "Immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, hypotension, etc." Although it is generally accepted that the rapid onset of any 1 or combination of these symptoms after a SCIT injection suggests a more severe reaction, the timing of the onset of symptoms does not always correlate with the severity of symptoms as suggested in this grading system. The 1993 EAACI grade 4 is similar to the revised EAACI's grading system except the earlier grade 4 included the treatment required ("intensive "). The current EAACI grading system does not include treatment or response to treatment.

Another grading system, attributed to Portnoy, was included in the Allergen Immunotherapy: A Practice Parameter Second Update (see this article's Table E7 in the Online Repository at www.jacionline.org).[3] This system uses a 0 to 6 scale with 0 designating no reaction and 1 representing a local reaction greater than a "half-dollar." Grades 2 through 4 are somewhat organ-specific, with grade 2 cutaneous only and grade 4 associated with pulmonary symptoms.

The drawbacks of all of these grading systems are that the criteria used to define grade severities are either vague (eg, mild rhinitis or asthma or responding well to antihistamines) or too specific (eg, onset less than 15 minutes).

Although most reactions that occur within minutes of a SCIT injection may be severe and progress rapidly, severe and fatal SCIT reactions can also begin more than 30 minutes after the injection. In a case-control review of 388 patients who received a total of 10,497 SCIT injections, 48% of SR started more than 30 minutes after the injection.[21] The onset of symptoms was greater than 30 minutes after the injection in 3 of the 17 confirmed fatalies in a 2004 12-year survey of AAAAI members on fatal and near-fatal SCIT reactions.[10]

In general, using response to treatment in the criteria to define severity has pitfalls. Both severe and mild reactions may respond to epinephrine, and thus to stratify severity on the basis of response to therapy is not a very good discriminator—for example, severe reactions may respond well to the rapid administration of intramuscular epinephrine, or mild reactions, such as, rhinitis symptoms, may persist for some time after treatment. In addition, treatment of SCIT SRs is not uniform. Thus, a grading system that includes response to treatment may classify reactions with distinctly different severities a similar grade if they both respond well to treatment, such as rhinitis responding to oral antihistamine versus severe bronchospasm responding to intramuscular epinephrine. A grading system based only on symptoms avoids this pitfall.

The 1993 EAACI grading system is probably the most frequently used classification system for reporting safety results in allergen immunotherapy clinical trials throughout the world. However, some studies do not elaborate which of the 2 EAACI grading systems, 1993 or 2006, is used, or they report results as grade 2, 3, or 4 reactions with no specific reference to which classification system is used. One review, using the 1993 EAACI grading system to summarize the SCIT safety data, reported some of the 42 SRs as grade 0 (N = 7) or 1 (N = 26), which are grades that are not considered treatment-related.[22] A review that used the 2006 EAACI grading system comparing the safety of different cluster schedules reported that 16% of systemic adverse reactions were grade 0, which is defined as "no symptoms or nonspecific symptoms."[23]

Moreover, investigators of SCIT studies develop their own unique classification systems for grading SRs.[24] This variability and lack of uniformity in classifying SCIT SR make it impossible to compare the safety results in one trial versus another.

DEVELOPMENT OF THE NEW COLLABORATIVE WAO GRADING SYSTEM FOR SCIT SRS

An international Joint Task Force composed of members of the academic, clinical, and research allergy community was formed to develop a universal grading system for immunotherapy SRs. Existing grading programs formed the template for the grading system. In addition to information derived from the task force members' clinical experience, data from SR symptoms recorded in the literature and symptoms documented in fatal and near-fatal reactions were utilized.[10-12,16,25,26] Drafts of the SR grading system were circulated among participants, and the final draft was discussed at a WAO meeting in Paris in January 2009. Representatives from regional and national allergy societies, various international health care organizations, and the National Institute of Allergy and Infectious Diseases attended.

The WAO SCIT SR grading system is composed of 5 grades. Each grade is based on organ system involved and severity. Organ systems are defined as cutaneous, conjunctival, upper respiratory, lower respiratory, gastrointestinal, cardiovascular, and other. A reaction from a single organ system such as cutaneous, conjunctival, or upper respiratory, but not asthma, gastrointestinal, or cardiovascular is classified as a grade 1. Symptoms/signs from more than 1 organ system or asthma, gastrointestinal, or cardiovascular are classified as grades 2 or 3. Respiratory failure or hypotension, with or without loss of consciousness, defines grade 4 and death grade 5.The grade is determined by the physician's clinical judgment.

Unlike the multidisciplinary group's criteria for defining anaphylaxis, a symptom/sign representing a single organ system would be considered an SR in this grading system, as included in the epinephrine statement by the WAO.[14] Although this may appear to be inconsistent, the grading system applies specifically to situations in which a known allergen has been administered, whereas the multidisciplinary group's criteria apply to a broader spectrum of clinical situations and are intended to help determine whether anaphylaxis is likely to be present.

This grading system is a template that can be used by physicians and research investigators to grade SRs associated with SCIT or anaphylaxis induced by allergens or agents that cause nonimmunologic anaphylaxis. It can be modified, as necessary, when clinically assessing anaphylaxis to reflect more accurately time of onset; additional symptoms and signs recorded; medications, amount and time administered; position of patient at the onset versus when the patient was placed in the recumbent position; intravenous fluid, time, type, and amount; and other important parameters involved in the genesis, identification, and treatment of these reactions. Some reviewers have suggested a numerical grading system be used for various parameters—that is, a number for the severity, time of onset, time of administration of epinephrine, and whether intravenous fluids and medications were necessary. This too can be done when such numbers may more objectively differentiate these reactions.

The final grade will not be determined until the event is over. The final report should include the grade, which reflects the most severe symptom/sign, the first symptom(s)/sign(s), time of onset after the SCIT injection, and the timing of epinephrine administration, if administered. An alphabetical suffix can be used to denote whether and when epinephrine was or was not administered after the onset of symptoms: a, $\leq$ 5 minutes; b, >5 minutes-to $\leq$10 minutes; c: >10 to $\leq$ 20 minutes; d:>20 minutes; and z, epinephrine not administered. The following is an example of a final report of an SR with rhinitis followed by generalized urticaria beginning 10 minutes after the SCIT injection and epinephrine administered within 5 minutes of the onset of the initial symptom: Grade 2a; rhinitis: 10 minutes.

Consistent use of this 5-stage grading system in clinical trials and surveillance studies will allow better comparisons of SRs between different immunotherapy formulations and practice patterns. These, in turn, may help determine the best approach to treat SCIT SRs—that is, when to administer epinephrine.

The authors thank the following for their assistance in review and revision of this document: Stephen Durham, MD, Ira Finegold, MD, Stephen Kemp, MD, Phil Lieberman, MD, Gary Liss, MD, Hans-Jørgen Malling, MD, Noel Perez-Rodriguez, MD, John Oppenheimer, MD, Estelle Simons, MD and Dana Wallace, MD.

The authors and editors gratefully acknowledge Charu Malik, PhD for her administrative assistance.

The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System has been endorsed by the following organizations: the AAAAI, the Latin American Society of Allergy and Immunology, the Asia Pacific Association of Allergy, Asthma and Clinical Immunology, and the ACAAI.

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TABLE E1. Grading criteria used in the AAAAI/ACAAI Immunotherapy Safety Survey[E1]

Grade I: Mild SR: generalized urticaria *and/or* upper respiratory symptoms (eg, itching of the palate and throat, sneezing)
Grade 2: Moderate SR: asthma (eg, PEFR falls 20% to 40%) *with or without* generalized urticaria, upper respiratory symptoms or abdominal symptoms (nausea, cramping)
Grade 3: **Severe life-threatening anaphylaxis:** severe airway compromise because of severe bronchospasm (eg, PEFR falls more than 40%), *or* upper airway obstruction with stridor and/or hypotension

PEFR, Peak expiratory flow rate.

TABLE E3. SRs reported with SCIT and skin testing with aeroallergens and venom in some publications from 1995 to 2009

P/R*	Author (year)	Location	Duration of observation period	Schedule allergen	No. of patients/ no. of injections	SR rate		Time (min) (range)
						Patients (%)	Injections (%)	
R	Phillips[E2] (2009)	USA	6 mo	Conventional inhalant and venom	883/14,000	17 (1.9)	18 (0.13)	20 (1-60 min)
R	DaVeiga[E3] (2008)	USA	July 2002-March 2007	Conventional inhalant	830/9,659	15 (1.8)	36 (0.37)	50% <30 min, 8% >1 hour All severe reactions <30 min
R	Rank[E4] (2008)	USA	2004-2006	Conventional inhalant	338/10,497	25 (7.4)	29 (0.28)	48% >30 min, appeared at least as severe as SR<30 min
R	Roy[E5] (2007)	USA, multicenter	2 y	Conventional inhalant	12,963/1,108,621	258 (2)	283 (0.026)	ND
R	Harvey[E6] (2004)	USA	January 1997-July 2002	Rush inhalant	65	25/65 (38)	Does not apply	5 Moderate 20-45 min 1 severe started mild at 55 min
P	Tinkelman[E7] (1995)	USA	January-December 1991	Conventional inhalant	4,512/156,800	96 (2.1)	98 (0.06)	All severe reactions <30 min
R	Brehler[E8] (2000)	Germany	2-day 9 injections	Rush venom	403/3,627	43 (10.7)	ND	ND
R	Serrano[E9] (2009)	Spain, multicenter	1996-2006	Cluster depot inhalants	1,147/6,982	39* (3.4)	42* (0.6)	23% <30 min (10-360)†
P	Schiappoli[E10] (2009)	Italy, multicenter	Up to 2006	Depot	1,738/60,785	57 (3.28)	95 (0.156)	44% <30 min (1 grade 4), 56% >30 min (span 45 min-24 h)
P	Winther[E11] (2006)	Denmark	3 y	Depot, modified cluster	1,038/23,047	341 (32.8)	582 (2.5)	50% <30 min (all grade 4 were <30 min), 50% >30 min
P	Moreno[E12] (2004)	Spain, multicenter	1996-1997	Conventional inhalant	423/17,526	18 (3.7)	53(0.3)	All <30 min, except 2 AD flares
R	Ragusa[E13,E14] (1997, 2004)	Italy	1981-1990 1991-2000	Conventional inhalant	4,000/435,854	115 (5.2) 26 (1.1)	115 (0.06) 26 (0.01)	Almost all SR within 30 min
R	Gastaminza[E15] (2003)	Spain	5 y	Conventional inhalant and venom	1,212/29,762	60 (5)	79 (0.27)	73% <30 min
R	Akcakaya[E16] (2000)	Turkey	1989-1997	Depot dust mite	88/5,760	12 (13.6)	12 (0.2)	Most <30 min
P	Bagg[E17] (2009)	USA	2007-2008	SPT ID testing	1,456	6 (0.4) 46 (3.2)	Does not apply	
R	Valyasevi[E18] (1999)	USA	January 1992-June 1997	SPT ID testing	16,505 269	5 (0.03)	Does not apply	4 <25 min, 1 at 75 min

ID, Intradermal skin testing; *ND,* no data; *P,* Prospective; *R,* retrospective; *SPT,* skin puncture/prick test.

*Including 7 grade 0 reactions (nonspecific reactions).

†Time of onset of the one grade 3 reaction was 10 minutes. All others started later.

TABLE E4. Lockey et al[19] grading system

Severity	Symptom	SRI*
Severe	Unconsciousness	0.376
	Shock	0.376
	Drop in blood pressure	0.126
Moderate	Lower airway obstruction	0.050
	Upper airway obstruction	0.050
	Gastrointestinal symptoms	0.013
Mild	Angioedema/urticaria	0.003
	Pruritus	0.003
	Other	0.003
Possible score		1.000

SRI, Systemic reaction index, the numerical scale devised for ranking of severity of SRs. Signs or symptoms are each given a numerical ranking so that the sums of values for a mild reaction would not equal the lowest value of a moderate reaction, and the sum of values of moderate reaction, either alone or in conjunction with a mild reaction, would not equal the value of the least severe reaction.

TABLE E5. 1993 EAACI grading system for SCIT SRs[20]

Grading of systemic reactions within 30 min	
0 No symptoms	
1 Unspecific symptoms	Reactions probably not IgE-mediated, ie, discomfort, headache, arthralgia, etc.
2 Mild systemic reactions	Mild rhinitis or asthma responding adequately to antihistamines or β_2-agonist spray.
3 Non–life-threatening systemic reactions	Urticaria, angioedema, or severe asthma, responding well to treatment.
4 Anaphylactic shock	Rapidly evoked reaction of itching, flushing, erythema, bronchial obstruction, etc. requiring intensive treatment.

Types of systemic reactions after 30 min - 48 h
Unspecific symptoms
Urticaria
Eczema
Rhinoconjunctivitis
Angioedema
Asthma

State time of onset and termination of reaction after injections, eg, 3 h-2 d

TABLE E6. 2006 EAACI Grading of Severity for Systemic Side Effects[21]

Classification of systemic reactions	
0 No symptoms	No symptoms or nonspecific symptoms.
I Mild systemic reactions	Symptoms: Localized urticaria, rhinitis or mild asthma (PF <20% decrease from baseline).
II Moderate systemic reactions	Symptoms: Slow onset (>15 min) of generalized urticaria and/or moderate asthma (PF < 40% decrease from baseline).
III Severe (non–life-threatening) systemic reactions:	Symptoms: Rapid onset (<15 min) of generalized urticaria, angioedema, or severe asthma (PF >40% decrease from baseline).
IV Anaphylactic shock	Symptoms: Immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, hypotension, etc.

TABLE E7. Portnoy Method for Numeric Grading of Reactions to Allergen Immunotherapy[22]

Local	
0+ No significant reaction, or small area of erythema less than the size of a half dollar without swelling or wheal formation.	
1+ Erythema greater than the size of a half dollar and/or swelling or wheal formation.	
Systemic	
2+ Systemic reaction	Cutaneous only: may consist of a cutaneous eruption such as urticaria.
3+ Systemic reaction	Generalized pruritus and/or sneezing: may consist of increased allergy symptoms such as nasal congestion, sneezing, or pruritus especially in the mouth or throat.
4+ Systemic reaction	Pulmonary: consists of wheezing, shortness of breath, tightness. May be associated with decreased pulmonary function tests.
5+ Systemic reaction	Anaphylaxis: a sensation of not feeling right is a frequent prelude. May consist of hypotension, laryngeal edema, severe wheezing, and cramping.
6+ Cardiopulmonary arrest	